REMARKS

Rejections under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 26, 28-31, and 44-52 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide enablement for the full scope of the claims. The Examiner maintains that the specification "fails to enable any mouse other than a genetically modified mouse whose genome comprises a $Shp2^{flox}$ allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells...." *Office Action* at p. 3 (emphases added). The Examiner further states that "[t]he CaMK2a promoter drives expression only in the neurons of the hippocampus (see Reece 2004, page 388, provided herewith)." *Id.* at p. 3. The Examiner therefore asserts that "[e]vidence demonstrating that this promoter is expressed in all forebrain cells is necessary to address this rejection, given the teachings of Reece and the analysis set forth above." *Id.* at p. 4.

Applicants respectfully traverse. "A conclusion of lack of enablement means that ... the specification, at the time the application was filed, would not have taught one skilled in the art to make and/or use the full scope of the claimed invention without undue experimentation." *See M.P.E.P.* §2164.01(a), citing *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for a claimed invention. *See M.P.E.P.* § 2164.04. A specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See id.* Once the examiner has established a reasonable basis to question enablement, the burden falls on the applicant to present a persuasive argument that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See M.P.E.P.* § 2164.05. The evidence provided by applicant "need not be conclusive but merely convincing to one skilled in the art." *Id.* (underline in original). Applicants may cite references to show what one of skill in the art knew at the time of filing the application. *See id.*

Applicants respectfully submit that the Examiner has failed to establish a reasonable basis to question enablement of the pending claims, as the Examiner has not provided a sufficient reason to doubt the objective truth of statements in the instant Specification. Although the Examiner asserts that the Reece reference teaches that the CamK2a promoter drives expression

only in neurons of the hippocampus, Applicants point out that the Reece reference mischaracterizes the references it relies on to support this assertion. In particular, the Reece reference states that:

> ...the promoter of the calcium-calmodulin dependent kinase II (CaMKIIα) gene drives expression only in the neurons of the hippocampus (Mayford *et al.*, 1996). Such an approach works well, provided that a suitable tissue-specific promoter is available (Table 13.1).

Reece at p. 389 (emphases added). However, the Mayford *et al.* 1996 article cited in this passage teaches that "CaMKIIα is a serine-threonine protein kinase that is restricted to the forebrain (12-14). It is expressed in the neurons of the neocortex, the hippocampus, the amygdala, and the basal ganglia." *Mayford et al.* 1996, at p. 1678. The Mayford *et al.* 1996 article also teaches that the CAMKII promoter "can limit expression to forebrain neurons generally," and provides an example of a transgenic mouse with a CAMKIIα promoter that demonstrates "uniform [expression of a transgene of interest] throughout the forebrain, neocortex, hippocampus, amygdala, and striatum." *Id.*, at p. 1679.

Further, Table 13.1 of the Reece reference indicates that the Camk2α gene is expressed in "forebrain" cells, and cites to a Mayford *et al.* 1995 article that teaches that "[t]he α subunit of CaMKII is the most abundantly expressed isoform in forebrain structures such as hippocampus." *Mayford et al.* 1995 at p. 892 (emphasis added). The Mayford *et al.* 1995 article also teaches the generation of a transgenic mouse with a CamKIIα promoter that expresses a transgene "selectively in forebrain regions, in a pattern that was indistinguishable from that of the endogenous CaMKIIα gene, except that the transgene appeared to be reduced or absent from a medial layer of the cortex"—which one of skill in the art would recognize to include neurons of the neocortex (with the exception of a medial layer), the hippocampus, the amygdala, and the basal ganglia in view of the Mayford *et al.* 1996 article. *See id.* at pp. 892 and 893; *see also Mayford et al.* 1996 at p. 1678.

Applicants submit that one of skill in the art would understand the disclosure in the Mayfield articles, on which the Reece reference relies, teach that the CamK2a promoter drives expression in more than just neurons of the hippocampus. As such, it is not necessary for Applicants to provide evidence "demonstrating that this promoter is expressed in all forebrain

cells...given the teachings of Reece." *Office Action* at p. 4. Further, Applicants submit that one of skill in the art would have recognized that the generation of a mouse with a homozygous disruption of the Shp2 gene outside the forebrain may result in undesired phenotypes, and that this (as well as numerous other genetic modifications) is not the subject matter of the instant Specification or pending claims.

Applicants submit that the Examiner has therefore failed to meet the initial burden to establish a reasonable basis to question the enablement of the pending claims. However, even if the Examiner had met this initial burden, Applicants submit that one skilled in the art would have been able to make and use the claimed invention "using the application as a guide." *M.P.E.P.* § 2164.05.

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *M.P.E.P.* § 2164.01(b), citing *In re Fisher*, 427 F.2d 833 (CCPA 1970). The instant Specification teaches one of skill in the art to generate a genetically modified mouse with homozygous disruption of the endogenous Shp2 gene in the forebrain. In fact, Example 1 of the instant Specification provides a working example for generating such a mouse by breeding $Shp2^{flox/+}$ mice with CamK2a-Cre transgenic mice, and evidence that such mice exhibit a phenotype of interest. *See Specification* at Example 1, paragraphs [0031]-[0037], and Figures 1-7. As such, Applicants have provided convincing evidence that one of skill in the art would have been able to make and use the claimed subject matter without undue experimentation. In addition, Applicants submit that one of skill in the art at the time of filing would have known other tools for homologous recombination (*i.e.*, other than the Cre-loxP system) and other forebrain-specific promoters (*i.e.*, other than CamK2a). *See, e.g.*, Ng *et al.*, *Mol Ther* 3: 809-15 (2001) (submitted herewith as Exhibit 1); Gidoni *et al.*, *Transgenic Res* 10: 317-28 (2001) (submitted herewith as Exhibit 2); Hoang *et al.*, *Gene* 212: 77-86 (1998) (submitted herewith as Exhibit 3); Gao *et al.*, *PNAS* 101: 4661-66 (2004) (submitted herewith as Exhibit 4); and Backman *et al.*, *Nat Genet* 29: 396-403 (2001) (submitted herewith as Exhibit 5). As such, Applicants further submit that it is not necessary to narrow the claims to recite a $Shp2^{flox}$ allele or CamK2a-expressing cells as asserted by the Examiner.

Applicants respectfully submit that the full scope of the claims is enabled in light of the teachings of the Specification and the knowledge in the art at the time of filing of the instant application. Applicants therefore respectfully request that the Examiner withdraw the rejection of Claim 26 and claims dependent therefrom (*i.e.*, Claims 28- 31 and 44-52) under 35 U.S.C. § 112, first paragraph.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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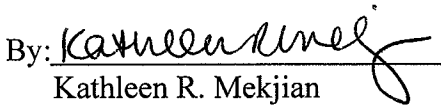
By: 

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